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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,804	09/12/2003	Gerold Schuler	1430/16	8361

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EXAMINER	
JUEDES, AMY E	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/661,804	SCHULER ET AL.	
	Examiner	Art Unit	
	AMY E. JUEDES	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12 and 25-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12 and 25-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/26/09, 7/24/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks, filed 11/23/09, are acknowledged.
Claim 24 has been cancelled.
Claims 12 and 33 have been amended.
Claims 12 and 25-33 are pending and are under examination.

2. The rejection of the claims under 35 U.S.C. 112 first paragraph is withdrawn in view of Applicant's amendment to the claims.

3. The rejection of the claims under 35 U.S.C. 102 and 103 are withdrawn in view of Applicant's amendment to the claims.

4. The following are new grounds of rejection.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12 and 25-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 is drawn to a method comprising contacting human blood comprising CD4+CD25+ regulatory T cells with antibodies specific for CD4/CTLA-4 or CD25/CTLA-4, and removing CD4+CD25+ regulatory T cells from the blood. It is not clear how the step of contacting with antibodies specific for CTLA-4/CD4 or CD25/CTLA-4 relates to the method of removing the regulatory T cells. Are said antibodies used to stimulate the cells in the blood, followed by a removal step with distinct reagents, or are the antibodies themselves used to sort and remove the regulatory T cells. Thus, it is unclear how the antibodies are to be used in the claimed method, since the only recited step involving the antibodies is a contacting step.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12 and 25-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method to remove CD4+CD25+ regulatory T cells comprising isolating a population of CD4+CD25+ T cells and testing the isolated CD4+CD25+ T cells for expression of CTLA-4 by contacting the cells with a CTLA-4 antibody,
does not reasonably provide enablement for:

a method to remove CD4+CD25+ regulatory T cells comprising contacting human blood comprising CD4+CD25+ regulatory T cells with antibodies specific for CD4/CTLA-4 or CD25/CTLA-4 and removing said CD4+CD25+ regulatory T cells from the human blood.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, *in re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

"The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention,

and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)" The MPEP further states that physiological activity can be considered inherently unpredictable.

The specification provides insufficient guidance to enable claims drawn to the method as broadly claimed. As an initial matter, it is noted that it is not clear how contacting with the CD4/CTLA-4 or CD25/CTLA-4 antibodies relates to the removal of CD4+CD25+ regulatory T cells. Thus, the claims are missing essential steps indicating how the CTLA-4 antibodies relate to the removal of CD4+CD25+ regulatory T cells. It appears that the claims encompass removing the CD4+CD25+ regulatory T cells by separating the cells that are bound to the CD4/CTLA-4 or CD25/CTLA-4 antibodies. However, CTLA-4 is primarily expressed as an intracellular molecule. In fact, CD4+CD25+ regulatory T cells in human blood only express intracellular CTLA-4, and do not express surface CTLA-4 (see Jago et al., 2004). Therefore, contacting human blood cells with a CTLA-4 antibody will not result in binding to CD4+CD25+ regulatory T cells in the absence of a step of permeabilizing the cell membrane, since said regulatory T cells only express CTLA-4 intracellularly. Thus, using a CTLA-4 antibody in a method of isolating functional CD4+CD25+ regulatory T cells, as is encompassed by the instant claims, is highly unpredictable.

Given the unpredictability of the art, the instant specification must provide a sufficient and enabling disclosure, commensurate in scope with the instant claims. The specification discloses specific examples of removing CD4+CD25+ regulatory T cells by purifying CD4+ T cell by negative selection, and contacting said CD4+ T cells with an antibody specific for CD25 to purify (i.e. remove) CD4+CD25+ regulatory T cells. Thus, the only guidance provided by the instant specification regarding the removal of CD4+CD25+ T cells is to select cells expressing CD4 and CD25 markers. The only examples provided relating to the use of CTLA-4 antibodies is to detect expression of CTLA-4 on already purified CD4+CD25+ T cell populations. No examples are provided in which CD4/CTLA-4 or CD25/CTLA4 antibodies are used to remove CD4+CD25+

regulatory T cells, as is encompassed by the instant claims. In fact, the instant specification on pages 11-12 discloses that CD4+CD25+ regulatory T cells in human blood do not express CTLA-4 at the surface. While the instant specification demonstrates that CTLA-4 is expressed intracellularly in regulatory T cells, an antibody can not bind to intracellular CTLA-4 in the absence of a permeabilization step, which is not recited in the instant claims. Furthermore, the instant claims are drawn to removing CD4+CD25+ regulatory T cells, and further testing said T cells in functional assays. Permeabilized T cells would not function in said assays. Thus, given the unpredictability of the art and the lack of guidance provided by the instant specification, it would require undue experimentation to use a CTLA-4 antibody in a method of removing CD4+CD25+ regulatory T cells as broadly claimed.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Koulis et al., February 2001, in view of Read et al., 2000 (both of record) and Leung et al., 1995.

Koulis et al. teach a method for isolating (i.e. removing) CD4+CD25+ regulatory T cells from human peripheral blood comprising isolating a PBMC population from total blood, and isolating a population of CD4+CD25+ T cells from said PBMC population. Since PBMCs comprise CD4+ T cells, said PBMC population is a population of CD4+ T cells from the blood, as recited in the instant claims. Koulis et al. also teach that the CD4+CD25+ T cells suppress the proliferation of T cells in a co-culture experiment in a cytokine independent manner.

Koulis et al. do not teach testing the CD4+CD25+ T cells for constitutive expression of CTLA-4.

Read et al. teach that intracellular CTLA-4 is constitutively expressed by CD4+CD25+ regulatory T cells in mice, and that it plays a role in their suppressive function. Leung et al. teach antibodies that can be used to measure CTLA-4 expression in human T cells.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to test the human regulatory T cells of Koulis et al., for the expression of CTLA-4, as taught by Read et al. and Lueng et al. The ordinary artisan at the time the invention was made would have been motivated to do so in order to determine if human regulatory T cells constitutively express CTLA-4, as is the case in mouse regulatory T cells. Furthermore, the ordinary artisan would have had a reasonable expectation of success in testing for CTLA-4 expression, since Leung et al. teach antibody reagents that can be used to measure CTLA-4 expression in human T cells.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, whose telephone number is 571-272-4471. The examiner can normally be reached on 8am to 4:30pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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